REMARKS

By this Amendment, Claims 4, 5, 13 and 22 are amended. Claims 17, 45 and 46 are canceled. Claims 1, 3-10, 12-19, 21-35, 48 and 49 are pending in this Application. Support for the amendments can be found in the previous claims. No issue of new matter arises. Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the March 30, 2006 Office Action, readdressed in the August 10, 2006 Advisory Action and respectfully request allowance of all pending claims.

Rejections under 35 U.S.C. §112, second paragraph

Claims 22 and 23 were rejected under 35 U.S.C. §112, second paragraph. Claim 22 was rejected as lacking antecedent basis for "complex". Claim 22 is amended to obviate this rejection. Claim 23 was rejected relating to the preamble of claim 22 and the term complex. Amendment to claim 22 is believed to obviate this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 5 was rejection relating to Hodgkin's Disease. Claim 5 as amended no longer recites Hodgkin's Disease. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 5 was also rejected relating to the placement of commas. Claim 5 is amended to incorporate commas as suggested by the Examiner to correspond *ipsis verbis* with the specification. Reconsideration and withdrawal of this rejection are respectfully requested. The Examiner opines that the two commas indicate two or three items. This interpretation is in error. The commas merely separate the interjected adjectival expression "follicular reticulum" for the "lymphoid tissue type" "cell sarcoma". The commas might be found distracting and are not deemed to be necessary. However, the interjected expression serves to more clearly describe Applicants' intended meaning. If the Examiner is not in agreement, the Examiner is respectfully requested to provide a detailed interpretation of what the two items are and why in his opinion one skilled in the art would have understood the specification to have that meaning.

Claim 13 was rejected based on an uncertainty of the Examiner. Whether the listed diseases are considered by the Examiner to be auto-immune is irrelevant. The diseases are not changed by the categorization. The Examiner admits uncertainty. Doubts on the part of the Examiner are not proper grounds for rejection. A proper interpretation of such issues would be to allow the Applicants to be their own lexicographers. Uncertainty should be resolved in favor or Applicants.

See, e.g., 35 U.S.C. §102: "A person shall be entitled to a patent unless-". If this rejection is maintained, Applicants respectfully request an affidavit from the Examiner under 37 CFR 104(d)(2) so that Applicants may avail their right to contradict or explain the Examiner's take on the issue. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph: enablement

Claims 3-10, 12-19, 21and 49 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse each and every allegation. The most salient aspects, in Applicants understanding, raised in the Office Action in support of this single rejection are noted below.

The rejection was presented in four parts.

I. Claims 4-10 relating to treatment of cancerous hyperproliferative disorders.

II. Claims 12-14 relating to non-cancerous hyperproliferative disorders.

III. Claim 1 (not a method claim and not rejected under 35 U.S.C. §112, first paragraph).

IV. Claims 15-19 and 21 relating to prevention of apoptosis.

The Examiner appears to rely on a *per se* rule that treatment of cancers and hyperproliferative disorders cannot be considered enabled. The Office Action argues that treating hyperproliferative disorders and preventing or suppressing apoptosis are opposing utilities.

Claim 17 is canceled.

Applicants agree that in at least one respect apoptosis and hyperproliferation are opposite; apoptosis results in fewer cells while hyperproliferation increases cell number. However, both apoptosis and hyperproliferation share a similarity of requiring a degree of cell cycling. Thus inhibiting CDKs can reduce apoptosis and inhibiting CDKs can also inhibit hyperproliferation. See part R. below. The utilities might be said to be opposing, but that does not take away from the fact that CDKs are involved in each process. Reconsideration and withdrawal of this rejection are respectfully requested.

The Office Action cites four cases alleged to be of particular relevance to enablement and treatment of cancers broadly. However, case law relates to law not to science. Law should be rather immutable, but skills of a scientist are not. As the skill in the art improves and the understanding of the science increases, what was not enabled years back may be enabled today. Thus these cases

cannot be properly relied upon for teachings of the skills in the art as of the filing date of the present application. To the extent that outdated teachings of the level of skill in the art are relied upon for making and maintaining this rejection Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner continues to rely upon sheer numbers of compounds as a basis for maintaining the rejection. The Examiner indicates that this is but one factor and states that a large number of members in a genus "must be a factor in the direction of lack of enablement". However, this factor is mitigated by the representative data presented relating to numerous compounds. The Examiner coldly dismisses this with a comment that the representative data "in no way limits the scope of the claims." Applicants agree: the scope of claims is not limited to examples; Applicants further assert that the data presented in the tables demonstrate by numerous representative examples, the properties to be attributed to the claimed genus. With respect to the recited -Ra portion, the Office action acknowledges many embodiments, but fails to acknowledge that each of the claimed embodiments can be classified as an embodiment reducing the basicity of the nitrogen to which the -Z- is attached. When the common characteristics of the group(s) in question are appreciated not issue of undue experimentation arises.

The Office Action contains cryptic comments relating to the –*Z*-Ra portion of the molecule. Applicants agree that the –Z-Ra portion of the molecule is not irrelevant. The –Z-Ra portion is crafted to reduce basicity of the nitrogen to which the portion is attached. Although the number of radicals that achieve this result is large, as a group they achieve the identical result. This is an argument for enablement because it goes to the representativeness of the examples shown in the tables. Regarding the allegation made that no evidence is presented. Applicants respectfully refer to Table 6 (page 170). The Examiner is respectfully requested to produce an affidavit under 37 CFR 1.104(d)(2) stating his reasons that the examples are not adequate to represent the genus.

A. At pages 8-11 CNS cancers are listed and discussed. This section of the Office Action concludes with the statement: "And there are many, many others." The size of a list the Examiner chooses to put together is no indication of a requirement for undue experimentation. All the listed diseases share a property of cell hyperproliferation. Indeed in the Office Action not one of these is noted to be free of hyperproliferation. Accordingly, antiproliferative agents as claimed in the present application would be expected to have a negative effect on proliferation of the cells of these cancers.

B. At page 11, the Office Action notes a connection between a leukemia and, e.g., Down syndrome. Other causes are mentioned. However, despite the multitude of causes each of these diseases is termed "leukemia", in reference to similarities of the disease. One similarity leukemias share is hyperproliferation. Thus an agent that is antiproliferative would be antiproliferative with respect to the genus of leukemias.

C. The Office Action lists several carcinomas of the liver. Each of these involves hyperproliferation. Thus listing the hyperproliferative conditions is supports use of antiproliferative agents such as described in the instant application merely serves to emphasize the breadth of effect the present invention can be expected to demonstrate.

D. Lung cancers are discussed at pages 12 and 13. These cancers all share hyperproliferation. Thus an antiproliferative agent such as described in the instant application would counter the disease. The robustness of the present invention is further demonstrated with each additional listing of hyperproliferative diseases.

E. Several thyroid cancers are listed. These all involve hyperproliferation. Comments above, e.g., relating robustness of the instant invention apply.

F. At pages 13 and 14 Carcinomas of the skin are listed including several family of the disease. These diseases are classified together because they share many attributes, including involvement of hyperproliferation. Robustness of the antiproliferative aspects of the instant invention is further demonstrated.

G. At page 14, colon cancers are discussed. The category is described as being diverse. Although diverse, each involves hyperproliferation. Antiproliferative actions would be expected to counter each and every disease here discussed.

H-N. Renal carcinomas, carcinomas of the prostate, penile carcinoma, carcinomas of extrahepatic bile ducts, breast cancers, ovarian cancers and cervical cancers are listed and discussed on pages 14-19. Although the primary location of the diseases varies, each disease involves hyperproliferation. Thus an antiproliferative treatment would be expected to counter each disease's process. Antiproliferative procedures would be expected to counter the hyperproliferation involved in each of these disease states.

O. At pages 19-21 hyperproliferative disorders as a class are discussed. By the very name, inhibition of proliferation would be expected to be beneficial. The robustness of the present invention is thus further demonstrated.

P. Autoimmune diseases are discussed. Some involve hyperproliferation. There is apparent controversy relating to others. To the extent that hyperproliferation is involved, the present invention provides antiproliferative agents and methods to counter the disease. To the extent that hyperproliferation might not be active in some disease states, the skilled artisan would be aware or could determine such without undue experimentation. No issue of enablement is implicated.

Q. At page 22, the Office Action discusses restenosis. Several etiologies are presented that might not involve hyperproliferation. However, no issue requiring undue experimentation is implicated. To the extent that angiogenesis involves cell growth and cycling, the present compounds by inhibition of cyclin dependent kinases have been demonstrated to control such growth.

R. The Office Action discusses various categorizations of apoptosis. Applicants acknowledge that apoptosis in different cells under different conditions may exhibit different properties. However, despite the way categories may be split they all refer to apoptosis.

> Pharmacological inhibitors of CDKs are currently being evaluated for therapeutic use against cancer, alopecia, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke), cardiovascular disorders (restenosis), glomerulonephritis, viral infections (HCMV/HIV/HSV) and parasitic protozoa (Plasmodium)

"A number of recent studies have pointed out that in addition to being an inhibitor of cell proliferation, p21 acts as an inhibitor of apoptosis in a number of systems, and this may counteract its tumor-suppressive functions as a growth inhibitor." Gartel, Andrei L. and Tyner, Angela L. Review: The Role of the Cyclin-dependent Kinase Inhibitor p21 in Apoptosis. *Molecular Cancer Therapeutics,* Vol. 1, 639-649, June 2002.

The article further states: p21 Is a Negative Regulator of p53-dependent Apoptosis . . .

> In response to radiation and chemotherapy, p53 protein is stabilized and mediates apoptosis and cell cycle arrest. Whereas the mechanisms of p53-dependent apoptosis are not well understood, p53-dependent cycle arrest is primarily mediated by the CDK inhibitor p21. There is a mounting evidence that p21 is a major inhibitor of p53-dependent apoptosis (Fig. 1). It is not entirely clear how a cell chooses between apoptosis

and p21-dependent cell cycle arrest after DNA damage and stabilization of p53, but often high levels of p21 expression mediate cell cycle arrest and protect from p53-dependent apoptosis.

And:

p21 Is a Negative Regulator of p53-independent Apoptosis

Multiple research articles confirm the advantageous apoptosis limiting effects of CDK inhibition. For example, the abstract of Hauck *et al. Circulation Research,* 91:782, 2002 states:

> Apoptotic cell death is an important mode of cell loss contributing to heart dysfunction. To analyze the importance of the E2F-dependent regulation of gene transcription in cardiomyocyte apoptosis, the function of cell cycle factors impinging on the retinoblastoma protein (pRb)/E2F pathway was investigated. In isolated neonatal ventricular myocytes, apoptotic cell death induced by hypoxia (deferoxamine, 100 μmol/L) specifically activated cyclin-dependent kinases (cdks) 2 and 3. Apoptotic cell death was inhibited by ectopic expression of cdk inhibitors $p21^{CIP}$ and $p27^{KIP1}$ but not $p16^{INK4}$. In addition, apoptosis was also abrogated by forced expression of kinase dead mutant proteins of cdk2/3 but not of cdk4/6. Introduction of cdk inhibitors or dominant-negative cdk2/3 blocked pRb hyperphosphorylation and abrogated E2F-dependent gene transcription, including that of the E2F-responsive genes of proapoptotic caspase 3 and caspase 7.

Thus cyclin dependent kinase inhibitors are known to negatively regulate, i.e., inhibit apoptosis; mechanisms relating e.g., to caspases 3 and 7 are shown to be related to CDKs. Thus, although the Examiner sees "opposing utilities", a more thorough examination of the science shows that CDK inhibition inhibits hyperproliferation, but also inhibits apoptosis. Applicants respectfully request that this rejection be withdrawn. To the extent that there may be CDK independent mechanisms of apoptosis in some cells under some conditions, Applicants respectfully submit that only routine. not undue experimentation would be required to identify such non-working embodiments, if in fact they do exist.

Regarding "Breadth of Claims", the Office Action has provided a generous resource listing various hyperproliferative diseases. This compendium serves as a list of many of the diseases that can be treated by use of antiproliferative agents. No valid reason is presented to call in doubt that inhibition of cell cycling, a necessary part of hyperproliferation, would not be operative in any of the listed diseases. For example Sigma Aldrich (extracted from www.sigmaaldrich.com/sigma/rbi-handbook/rbibook5_cdks.pdf) states:

> Pharmacological inhibitors of CDKs are currently being evaluated for therapeutic use against cancer, alopecia, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke), cardiovascular

disorders (restenosis), glomerulonephritis, viral infections (HCMV/HIV/HSV) and parasitic protozoa (Plasmodium)

Thus it is apparent that the art recognizes broad application of CDK inhibition.

(2) At page 25 the Office Action addresses predictability in the art. Predictability in the art is at a state where proliferation, including hyperproliferation is known to require active cell cycling. Inhibition of cyclin dependent kinases is predicted to inhibit cell cycling and thus inhibit hyperproliferation. While the scope of enablement might vary inversely with unpredictability of the factors involved, in the present instance, cell cycling is predictable. Pathways susceptible to inhibition of cell cycling are characterized. Accordingly, the very predictability relating to cell cycling and predictability thereof provides strong reasoning that the scope of enablement in the present instance is rather broad. A CCPA case is cited as instructive that physiological activity is generally considered an unpredictable factor. This was a general statement made years ago. The CCPA was dismantled 25 years ago. While some progress still needs to be made in understanding physiology, predictability is vastly improved. That the Patent Office has to rely on such out outdated caselaw is indicative of the weak basis underlying this rejection. Reconsideration and withdrawal of this rejection is deemed proper.

(3) With respect to dosage and guidance, the Office Action notes that a suggested range of dosage is generic to all diseases. This guidance is alleged to be of little value. However, no issue of undue experimentation arises. The Office Action observes that "many promising anti-cancer drugs have foundered because of an inability to find a dosage regimen that actually works". However, the standard of working is not stated. Applicants believe that the anti-cancer drugs in question may have foundered in the Food and Drug approval process because of a narrow balance between safety and efficacy. The Office Action chastises Applicants as being illogical for stating the obvious based on the Examiner's allegation. Applicants presume that "many" refers to a significant number. If "many" is not significant, then only minimal problems are implicated. If many means a significant number, then the practice is obviously routine and cannot be characterized as undue. Applicants respectfully restate that the basis for an enablement rejection is a requirement for undue experimentation to practice the claimed invention. Caselaw makes clear that not every embodiment conceived must be a working embodiment, only that the skilled artisan can arrive at a working embodiment without undue experimentation. Reconsideration and withdrawal of this rejection is thus deemed proper.

A CCPA case is cited as instructive that physiological activity is generally considered an unpredictable factor. This was a general statement made years ago. The CCPA was dismantled 25 years ago. While some progress still needs to be made in understanding physiology, predictability is vastly improved. Profound advances can be found in the medical literature. The cell cycle is better understood. Involvement of cyclin dependent kinases and effects of inhibition thereof are now known. Unpredictability is thus minimized as an issue. That the Patent Office has to rely on such out outdated caselaw opining on the state of the art decades past is indicative of the weak basis underlying this rejection.

(4) State of the prior art is discussed at pages 26-27. The Examiner observes that compounds of similar structure that inhibit cyclin dependent kinases are unknown in the literature for treatment of hyperproliferative disorders. Someone has to pioneer a field. The present Applicants have made pioneering contributions to this art recognizing benefits of inhibiting cyclin dependent kinases and providing novel compounds that inhibit them. While perhaps Applicants cannot piggy-back on past successes of others, Applicants have not set out to claim a me-too type of pharmaceutical. Public policy should also encourage novel approaches' such as instantly described and claimed.

(5) The Office Action notes no working examples for treatment of actual disease. However, disease models are effectively inhibited from cell culture experiments. Claims specify three CDKs. Inhibition of these is demonstrated in the application to effect inhibition of cyclin dependent kinases. Inhibition of other CDKs is expected to have similar effect. The Examiner has provided not rationale why such should not be the case. Methotrexate is a compound with a similar but not identical mechanism. Please provide an affidavit under 37 CFR 1.104(d)(2) detailing the special knowledge and supporting data possessed by the Examiner to support this rejection.

(6) Skill in the art is discussed at pages 26-36. Assertions, insinuations and speculations are rampant. For example, the Office Action states that no compounds have been found to treat cancer generally. However, many compounds are used in more than one cancer. Just because no compound is deemed "best" for all cancers does not mean that general applicability does not exist. With respect to autoimmune diseases, Applicants respectfully submit that methotrexate has been found to be of general benefit, e.g., for many autoimmune disease, and accordingly is a treatment of choice for a number of distinct autoimmune diseases, e.g., rheumatoid arthritis.

Applicants respectfully submit that there are different standards applied by the Food and Drug Administration and other agencies. Lack of FDA approval of a compound has never been grounds

to invalidate a claim. The law does not provide such a standard. Accordingly Applicants respectfully submit that it is improper for the Office now to require treatment of a disease (phase II or II trials) before a patent can be issued. A list of cancers is again included. Each of these has a common thread of involving hyperproliferation, the very activity inhibited according to the present invention.

Skill level relating to smooth muscle hyperproliferative disorders is characterized as very low. Tell that to Dr. Maurer's patients! Even if causes of events may not be known, the events and activities involved in the events can still be understood. The Office Action notes that treatment has been ineffective using hormones, etc. with methods of action unrelated to those of the present application. How this relates to the present compounds and there proven activities is not understood by Applicants.

The Office Action bases this rejection in part on the omission in the specification of B-cell involvement in antibody production. This again demonstrates the weakness of the Office in supporting and sustaining this rejection. Does the Examiner mean to indicate that B-cells do not make antibodies or that B-Cells do not proliferate, or that they proliferate by a cell cycle independent mechanism[1]? Applicants are not required to list all truths in a patent application. Reconsideration and withdrawal of this rejection are deemed proper.

The Office Action refers to "cells" and asserts that "it covers all three types". First, Applicants believe that "types" does not refer to "cells" because there are more than three types of cells. Applicants cannot properly reply to the Office Action when meaning is unclear. Clarification is respectfully requested.

Applicants do not argue that it is improper to reject claims that have significant or substantial inclusion of inoperative embodiments. Applicants do not see the analogy to a reject under 35 U.S.C. §102 or 35 U.S.C. §103 however. A 35 U.S.C. §102 (anticipation) rejection requires that the entire claim be anticipated. Suppose a claim had 100 elements, a reference that showed 99 of the elements, but omitted only one could not properly be used to reject the claim. Similarly for a 35

U.S.C. §103 rejection, the reference or combination of the references must teach or suggest all the claim limitations. See below.

[1] If any of these are true, the Examiner is requested to provide a proper affidavit under 37 CFR 1.104(d)(2).

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143.

To make a rejection when only a single element is taught (("nearly all of the claim is not rejectable") is plainly a misapplication of the law!

Skrivan as related by the Examiner appears more of an essential elements case than an undue experimentation case. The language quoted in the Office Action however supports enablement of the present claims. "There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art to include those factors". *Atlas Powder* says it best: "[I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims indeed might be invalid." Here the word "unduly" appears, once again emphasizing the standard for assessing whether a claim is enabled is whether undue experimentation would be required to practice the claimed invention. With regard to the present claims, despite the pages of listings set forth in the Office Action, there is no evidence that undue experimentation would be required to practice the claimed invention. Several examples noted in the Office Action appear to demonstrate the routine nature of any experimentation that would be required.

"Reasonable doubt" is raised as a standard, but then we find that this standard is with regard to doubting utility. Applicants respectfully request that the utility rejection be made of record in a non-final Office Action so that a proper reply can be filed.

Applicants appreciate the Examiner's notation of an omission in the previous reply. Yes "not" was omitted. It should appear before "presumed".

At page 36, penultimate paragraph, Applicants note that the Examiner has misunderstood Applicants arguments. Applicants do not argue that inoperative embodiments are of no significance. Applicants' argument is that inoperative embodiments are tolerated so long as practicing the claimed invention, e.g., finding the next working embodiment does not require undue experimentation. Applicants hope that this clarification is helpful.

Applicants note that in view of the above comments and explanations, reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, enablement rejection would be deemed proper.

Double Patenting

Applicants gratefully acknowledge the Examiner's indication of a double patenting issue. However, the claims have yet been deemed allowable, the final form and number of the claims that might issue in this application is unknown. A terminal disclaimer at this time is premature as any claim(s) that might issue may or may not be deemed obvious over claims 1-10 of USP 6,861,524.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt indication of such. Should the Examiner wish to suggest additional amendments that might place the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

Respectfully submitted,

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